Haloperidol does not affect middle-latency auditory fields in healthy subjects

S. Kähkönen[1,2,5], J. Ahveninen[2], E. Pekkonen[1,2,3], S. Kaakkola[3], J. Huttunen[4], T. Peltonen[2],
R.J. Ilmoniemi[1], and I.P. Jääskeläinen[2]

[1]*BioMag Lab., Medical Engineering Centre, Helsinki University Central Hospital, P.O. Box 442, FIN-00029 HUS, Finland;* [2]*Cognitive Brain Research Unit, Dept. of Psychology, University of Helsinki;*
[3]*Department of Neurology, Helsinki University Central Hospital, Helsinki;*
[4]*Department of Clinical Neurophysiology, Helsinki University Central Hospital, Helsinki;*
[5]*Department of Psychiatry, Helsinki University Central Hospital, Helsinki*

1 Introduction

Haloperidol is a potent, partially selective dopamine D_2 receptor antagonist, which has been widely used in the treatment of psychotic disorders. A single dose of haloperidol alters glucose utilization in subcortical and cortical areas studied with positron-emission tomography (PET) in healthy subjects [1]. Spontaneous EEG activity was measured after 3 mg of haloperidol administration and increase in slow waves (delta and theta) and decrease in alpha and beta activity was observed [2].

Magnetoencephalography (MEG) measures extracranial magnetic fields produced by ionic current flow generated mainly by cortical pyramidal cells. MEG offers a non-invasive method to study brain function with high temporal resolution and enables accurate source localization [3]. The synchronous activity of large neural populations can be studied with auditory evoked magnetic fields (AEF), time-locked to the presentation of auditory stimuli. The earliest cortical AEF, the middle-latency AEF (MAEF) occurs about 20-70 ms from the stimulus onset. The MAEF is composed of several distinct deflections, with P_am peaking at approximately 30 ms and N_bm at about 45 ms.

The present study investigated auditory processing in healthy volunteers after D_2 receptor antagonist haloperidol administration by recording the P_am and N_bm components of MAEFs.

2 Methods

2.1 Subjects and procedure

In a double-blind, randomized, placebo-controlled, cross-over study design, the dopamine D_2-receptor antagonist haloperidol (Serenase® 1 mg, Orion Pharma Pharmaceutical Company, Espoo, Finland) 2 mg or placebo was given orally to 12 right-handed healthy volunteers (aged 20-28 years; six females) after informed written consent and institutional ethical committee approval were obtained. The drugs were administered 3 h before the recording. The subjects were instructed to avoid alcohol for at least 48 h, and caffeine and tobacco for 12 h prior to MEG recordings. The subjects reported having no history of neurological or psychiatric disorders or using any drugs for 2 weeks before the study. None had been exposed to any class of neuroleptics previously. The hearing level was confirmed by measuring auditory threshold with the auditory stimulator used for this experiment. All experimental sessions were carried out between 8 a.m. and noon, and the sessions were separated by one week.

2.2 Stimulus and data acquisition

During the MEG recording, the subject sat in a comfortable chair in a magnetically and electrically shielded room (Euroshield, Eura, Finland). The AEFs were recorded with 122-channel MEG (Neuromag, Helsinki, Finland; [4]). Click stimuli (0.1-ms duration) were presented to the left ear, delivered at a 10-Hz rate at 60 dB above an individually measured hearing threshold. During the stimulation, the subjects were instructed to concentrate on viewing a video film of their own interest, and to ignore the clicks. Each two-channel sensor unit measured two independent magnetic field gradient components $\partial B_z/\partial x$ and $\partial B_z/\partial y$, the z-axis being normal to the local helmet surface. The position of the subject´s head relative to the recording instrument was determined by measuring the magnetic fields produced by marker coils in relation to cardinal points of the head (nasion, left and right pre-auricular points), determined before the experiment using an Isotrak 3D-digitizer (Polhemus, Colchester, VT, U.S.A.) [5]. In addition, vertical and horizontal electro-oculograms (EOG) were recorded.

The recording passband was 1-250 Hz for MEG, sampling rate was 1 kHz. Digital band-pass filtering was performed off-line at 10-120 Hz [6]. The analysis period was 150 ms (including a 50-ms prestimulus baseline). The first few responses and all the epochs coinciding with EOG or MEG changes exceeding 150 µV or 3000 fT/cm, respectively, were omitted from averaging. At least 1000 artefact- free responses were recorded and averaged.

2.3 Data analysis

The AMF peak latencies and amplitudes were measured from the channel pair showing the highest-amplitude responses (the amplitude being determined as $|a| =[(\partial B_z/\partial x)^2 + (\partial B_z/\partial y)^2]^{1/2}$), separately for the left and right temporal areas. The AMF sources were localized with single equivalent current dipole (ECD) modeling, found by a least-squares fit using a fixed subset of 34 channels separately over each auditory cortex [3]. Dipole fits with at most 30% residual variance were considered successful. The statistical analysis was carried out with two-factor (drug x hemisphere) repeated-measures ANOVAs.

3 Results

Click stimulation elicited prominent P_am and N_bm responses. Neither the peak latencies nor the peak amplitudes of the MAEF components were significantly affected after haloperidol administration over either hemispheres measured (Table 1). The source locations of the responses were not significantly influenced by haloperidol.

Table 1. *Mean ± SD peak latencies and amplitudes of P_am and N_bm*

		Haloperidol	Placebo
P_am (contralateral)	Amplitude (fT/cm)	5.6 ± 2.3	5.6 ± 2.3
	Latency (ms)	30 ± 3	29 ± 2
P_am (ipsilateral)	Amplitude (fT/cm)	6.3 ± 2.0	5.4 ± 2.1
	Latency (ms)	30 ± 2	29 ± 3
N_bm (contralateral)	Amplitude (fT/cm)	6.4 ± 2.2	6.5 ± 2.6
	Latency (ms)	47 ± 4	47 ± 3
N_bm (ipsilateral)	Amplitude (fT/cm)	5.1 ± 1.5	5.2 ± 1.5
	Latency (ms)	48 ± 4	47 ± 3.5

4 Discussion

Whole-head MEG was used to determine the effects of an acute haloperidol challenge on brain magnetic fields using auditory clicks in healthy subjects. A single low dose of haloperidol (2 mg) did not affect middle-latency auditory cortical responses. These results suggest that dopamine D2-receptors are not involved in the early phases of cortical processing of auditory information.

Only a few previous studies have been devoted to the effects of haloperidol on evoked potentials. Our results are in line with the findings of Kudoh and Matsuki (1999) [7], who studied the effects of another dopamine D2-receptor antagonist droperidol on MAEP during total intravenous anesthesia. Patients were injected diazepam, fentanyl, and ketamine with droperidol (0.1 mg/kg). MAEP did not differ before and after the administration of drugs. Similarly, the amplitudes or latencies of auditory N1 nor P1 were affected by the administration of 3 mg of haloperidol in healthy volunteers [8]. One study investigated the effects of haloperidol on visual potentials showing that P300 was delayed by haloperidol [9].

PET studies have shown that haloperidol alters metabolic activity in subcortical and cortical areas. Bartlett et al. (1994) showed with PET that 5 mg of haloperidol reduced glucoce utilization in the frontal, occipital, and anterior cingulate cortex, whereas the putamen and cerebellum showed significant increases. Deep sources, such as the postulated subcortical sources affected by haloperidol contributing to the MAEP [10], confound little the signal detected by MEG. This is due to the fact that the magnetic fields fall off more rapidly than the electric fields with increasing distance from the source. In addition MEG is most sensitive to tangential cortical sources [3] and to activity in the fissures, whereas EEG is sensitive also to radial currents, measuring the activity from the gyri. Hence it is possible that the change in electromagnetic activity following haloperidol administration in the gyri of cortex is not detected by MEG.

Results from both MEG and intracranial recordings have suggested that MAEFs are generated in the superior aspects of temporal lobes, in or near primary auditory cortex [11, 12, 13]. Recent histopathological studies have shown that the majority of dopamine D2 receptors were observed in the lateral and inferior aspects of the superior temporal gyrus, less frequently on the lateral surface of the inferior temporal gyrus and the parahippocampal cortices, and were absent from primary auditory cortex [14]. This could in part explain the present results.

Previously, only of few attempts to elucidate the transmitters involved in MAEP generation, the electrical counterpart of MAEF, have been performed. Brain acetylcholine has been shown to play an important role in the generation of the P_a response [15, 16]. In these studies, the P_a amplitude was enhanced by muscarine receptor antagonist scopolamine, and was reduced by the agonist physostigmine.

To our knowledge, this is the first measurement of magnetic responses to a haloperidol challenge in healthy subjects with no previous exposure to neuroleptics. In the future, a combined use of MEG and EEG will provide a more complex view of brain effects of haloperidol in healthy volunteers and in the clinical population.

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